REMARKS

Applicants have amended the title to more accurately describe the invention.

Applicants thank the Examiner for his review of the instant application. For the reasons stated below, the rejections of the presently pending claims are respectfully traversed. Claims 6-8 and 11-17 are presented for examination.

Status of the Claims

Applicants mailed an Amendment Filed with Notice of Appeal on January 5, 2006, cancelling Claims 4 and 5, and amending Claim 12 to change the claim dependency from canceled Claim 4 to Claim 6. On March 22, 2006, an Advisory Action issued entering these amendments. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Priority

The PTO asserts that because the disclosure of PCT/US00/23328 is not enabling for the instant invention, the filing date of the present application, May 7, 2002, is considered the priority date. For the reasons of record, Applicants maintain that the present application is entitled to at least the priority date of August 24, 2000.

Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of pending Claims 6-8 and 11-17 under 35 U.S.C. § 101 as lacking utility for the reasons set forth in the previous Office Actions. The PTO states that the specification discloses that the PRO1926 polynucleotide is more highly expressed in normal esophageal tissue as compared to esophagus tumor, and that Applicants have asserted the use of the polypeptide for diagnosis. However, the PTO rejects this utility, stating that "[t]here is no further supporting evidence to indicate that the polypeptide encoded by the polynucleotide of the instant invention is also differentially expressed in normal tissue compared to the tumor tissue and as such one of skill in the art would conclude that it is not supported by a substantial asserted utility or a well-established utility." *Final Office Action* at 4-5.

Applicants incorporate by reference their previously submitted arguments, including those made in the Appeal Brief, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the PTO has not met its burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However even if the PTO has met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1926 polypeptide is expressed at least two-fold higher in normal esophageal tissue as compared to esophagus tumor tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* a decrease, generally leads to a corresponding change in the level of the encoded protein, *e.g.* a decrease;

3. Given the differential expression of the PRO1926 mRNA in esophageal tumors compared to normal esophagus tissue, it is more likely than not that the PRO1926 polypeptide is also differentially expressed in esophageal tumors compared to normal esophagus tissue, making the claimed polypeptides useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making two arguments in response to Applicants' asserted utility:

1. The PTO challenges the reliability of the evidence reported in Example 18, stating for example that there is no guidance in the specification as to how high the expression levels are, and that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, citing Hu *et al.* for support;

2. The PTO cites Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71), Chen *et al.* (Mol. and Cell. Proteomics, (2002) 1:304-313) and Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30) to support its assertion that polypeptide levels cannot be accurately predicted from mRNA levels. Therefore, further research needs to be done to determine if the increase or decrease in PRO1926 cDNA expression supports a role for the peptide in cancerous tissue.

Applicants respectfully submit that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

Example 18 and the Grimaldi Declaration Establish that Differential Expression of mRNA is Sufficient to Provide Utility for the mRNA as a Diagnostic Tool

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1926 polypeptide in esophageal tumors is insufficient, and that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

The only objection by the PTO to the data in Example 18 that is supported by any reasoning or evidence is the assertion based on the Hu *et al.* reference that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The remainder of the objections is not supported by any evidence or reasoning as to why the data in Example 18 are insufficient, and therefore these unsupported objections cannot establish a *prima facie* case. *See In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence.") (emphasis added).

Despite the lack of evidence to the contrary, Applicants have previously pointed to the teachings of the specification and the first Grimaldi Declaration (submitted as Exhibit 2 in the Amendment and Response to Office Action mailed April 7, 2005) establishing that the teachings

of the specification are sufficient to establish that the PRO1926 gene is under-expressed in tumor cells compared to corresponding normal tissue. Applicants incorporate by reference the previous arguments, and will not repeat them here.

Regarding Hu, Applicants have previously discussed at length why Hu is directed to a known role in a disease, and is not relevant to the issue of whether the differentially expressed PRO1926 mRNA is useful as a diagnostic tool for cancer. Applicants incorporate by reference the previous arguments, and will not repeat them here.

In addition to the persuasive reasons articulated in Applicants' arguments of record, the PTO's reliance on Hu is also misplaced because Applicants are not relying on microarray data as discussed in Hu:

> In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study. *Hu* at 405, left column, first paragraph (emphasis added).

Instead, Applicants are relying on quantitative PCR analysis to measure gene expression levels. In a recent study by Kuo *et al.* (Proteonmics 5(4):894-906 (2005)), the authors used microarray analysis combined with proteomic analysis using two-dimensional gel electrophoresis to examine changes in gene expression in leukemia cell lines. The authors report that "[c]omparison of microarray and proteomic expression profiles showed poor correlation. Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction [RT-PCR], Western blotting and functional assays, on several genes and proteins, nonetheless, confirmed that there is indeed a good correlation between mRNA and protein expression." *Kuo et al.* at Abstract (emphasis added)(attached as Exhibit 1). Thus, even if accurate, Hu's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

In conclusion, Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1926 mRNA between esophageal tumors compared to normal esophagus tissue. Further, the teachings of Hu are not relevant to Applicants' asserted utility because Hu is directed to the sufficiency of microarray data in identifying genes with a known role in a disease, and Applicants have asserted that the claimed polypeptides have a diagnostic utility, based in part on the results of the PCR analysis of Example 18. Therefore, the only issue which remains is whether the data in Example

18 regarding differential expression of the PRO1926 mRNA are reasonably correlated with differential expression of the PRO1926 polypeptide such that the claimed polypeptides have utility as diagnostic tools as well. As discussed below, even if the PTO has established a reasonable doubt regarding Applicants' assertion that they are reasonably correlated, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level lead to corresponding changes in protein level.

The PTO's Evidence is Not Relevant to Determining Whether a Change in mRNA Level for a Particular Gene lead to Corresponding Change in the Level of the Encoded Protein

Applicants turn next to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1926 polypeptide in esophageal tumors, it is likely that the PRO1926 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic tools.

In response to Applicants' assertion, the PTO cites Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71), Chen *et al.* (Mol. and Cell. Proteomics, (2002) 1:304-313) and Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30) as support for its argument that "polypeptide levels cannot be accurately predicted from mRNA levels." The PTO also makes the argument that "it is noted that the features upon which applicant relies (i.e., changes in message levels are correlated to protein levels) are not recited in the rejected claim(s). Although claims are interpreted in light of the specification, limitations from the specification are not read into the claims." *Examiner's Answer* at 29.

As to the PTO's argument that the claims do not recite the feature being relied on, this argument fails because it misstates the law. Applicants do not need to recite any additional limitations to make arguments about what one of skill in the art would have believed regarding the utility of the claimed polypeptides. As explained above, Applicants are arguing that given the differential expression of the PRO1926 mRNA, one of skill in the art would believe that the PRO1926 polypeptide is also differentially expressed, and therefore one of skill in the art would believe that the asserted utility is more likely than not true. Applicants rely on the assertion that

it is well established in the art that changes in mRNA level lead to changes in protein level to support an asserted utility for the claimed polypeptides. This assertion does not need to be recited in the claims to be relied on to support Applicants' utility. The PTO cannot cite any statute, case law or M.P.E.P. section to support its argument to the contrary because no such requirement exists.

As to the PTO's cited references, Applicants have previously discussed at length why the Haynes, Chen and Gygi references are not relevant to the issue of whether changes in mRNA level for a particular gene lead to changes in protein level. Applicants incorporate by reference the previous arguments, including those made in their appeal brief, and will not repeat them here.

However, in an attempt to illustrate why references which relate to static global levels of mRNA and protein across different genes are not relevant to this issue, Applicants offer the following illustration and analogy with the understanding that like all illustrations and analogies, they are not perfect and therefore do not represent any admissions or binding statements regarding Applicants' disclosure or invention.

Haynes, Gygi, and portions of Chen all discuss whether there is a correlation between the static level of mRNAs and proteins globally, *i.e.* across different genes. This is equivalent to conducting a hypothetical Experiment 1, where a particular cell type has 100 copies of mRNA for gene X, 200 copies of mRNA for gene Y, and 400 copies of mRNA for gene Z. If there is a global correlation between static mRNA levels and protein levels across genes, the ratio of the amount of proteins X:Y:Z would be approximately 1:2:4. This is essentially what the cited references examined.

In contrast, Applicants are relying on a correlation between changes in mRNA level for a particular gene leading to a corresponding change in the level of the encoded protein. For example, in hypothetical Experiment 2, if gene X has 200 copies of mRNA per cell in condition A (*e.g.* normal), and 100 copies of mRNA for gene X in condition B (*e.g.* tumor), the ratio of the amount of protein X in condition A:B would be approximately 2:1, such that there is a correlation between the change in the level of mRNA and protein for a particular gene.

The PTO argues that because there is no correlation between static levels of mRNA and protein across genes, as illustrated by Experiment 1, one of skill in the art would not expect an increase or decrease in the amount of mRNA for a particular gene to result in a corresponding

change in the amount of the encoded protein, as illustrated in Experiment 2. This is simply wrong.

For example, Haynes reports that the amount of protein produced by similar levels of mRNA varied by as much as fifty-fold, and that similar amounts of protein were sustained by amounts of mRNA that varied by as much as forty-fold. *Haynes* at 1863, first full paragraph. Based on these results, Haynes concludes that "protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript." *Id.*

This is analogous to a finding that on one gallon of gas, a hybrid car can travel 70 miles but a large truck can only travel 5 miles, or that to travel 70 miles, a hybrid car requires 1 gallon of gas, but a large truck requires 14 gallons. That is to say, there are many things which affect the fuel efficiency of an automobile. Based on these observations, one could conclude that given the lack of correlation between the amount of gas in an automobile and the distance it travels, one cannot predict how far an automobile will travel based on the amount of gas in the tank.

Even if true, Haynes' data and conclusions are irrelevant to Applicants' assertion, which is that increasing or decreasing the amount of mRNA for a particular gene will result in a corresponding increase or decrease in the amount of the encoded protein. This is analogous to increasing or decreasing the amount of gas in an automobile – it will travel farther if you add more gas, and not as far with less. The fact that there are many things which affect fuel efficiency and therefore you cannot predict how far and automobile will travel without knowing if it is a hybrid or a large truck is irrelevant – both a hybrid and a truck travel farther on more gas, and not as far on less.

Similarly, Chen *et al.* report that plotting the level of mRNA for a particular gene against the level of the corresponding protein as measured across numerous samples, they found a lack of correlation for most genes studied. *Chen* at Abstract. However, with the exception of three genes reported in Figures 2A-2C, Chen does not indicate whether the level of mRNA varied significantly across samples, and Chen did not select samples or genes which were expected to vary across samples (*e.g.* normal versus tumor). Therefore, it is not known if Chen examined changes in mRNA level, or if the level of mRNA was unchanged. Therefore, the relevance of Chen's finding to Applicants' asserted correlation between changes in mRNA and protein is not known.

By analogy, if a person drives a particular car as far as possible on 5 gallons of gas 20 different times, and then plots the amount of gas against the distance driven, a lack of correlation between the amount of gas and distance is meaningless, and merely reflects systematic error in measuring the amount of gas and distance driven. Only if substantially different amounts of gas were plotted against their respective distances can you answer the question of whether increasing or decreasing the amount of gas results in increasing or decreasing the distance driven.

Applicants emphasize, and the PTO will recognize, that these are simplified illustrations to demonstrate the difference between the two issues being examined. However, these illustrations make clear that even if there is no correlation in the first experiment looking at static levels of mRNA and protein across genes, there can still be a correlation between changes in mRNA and protein for a particular gene as examined in the second experiment. As these illustrations make clear, the PTO's evidence simply is not relevant to answering the question of whether it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true.

Applicants' Evidence Establishes that a Change in mRNA Level for a Particular Gene lead to Corresponding Change in the Level of the Encoded Protein

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, a copy of the declaration of Paul Polakis, Ph.D., excerpts from the Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) and (4th ed. 2002), excerpts from the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)), a reference by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, and a reference by Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002). The details of the teachings of these declarations and references, and how they support Applicants' asserted utility, are of record and will not be repeated here.

In addition to the supporting references previously submitted by Applicants, Applicants submit the following references to further support the assertion that changes in mRNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

In a comprehensive study by Orntoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45) (previously submitted with IDS, attached hereto as Exhibit 2), the authors examined gene amplification, mRNA expression level, and protein expression in pairs of non-invasive and invasive human bladder tumors. *Id.* at Abstract. The authors examined 40 well resolved abundant known proteins, and found that "[i]n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations. Only one gene showed disagreement between transcript alteration and protein alteration." *Id.* at 42, col. 2. The alternations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

In a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 3) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 4) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in

20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 5) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 6) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20Salpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Maruyama *et al.* (Am. J. Patho. 1999; 155(3):815-22) (abstract attached as Exhibit 7) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that pancreatic cancer cell lines frequently coexpressed all three Ids, "exhibiting good correlation between Id mRNA and

protein levels." *Id.* at Abstract. In addition, the authors teach that all three Id mRNA levels were expressed at high levels in pancreatic cancer samples compared to normal or CP samples. At the protein level, Id-1 and Id-2 staining was faint in normal tissue, while Id-3 ranged from weak to strong. In contrast, in the cancer tissues "many of the cancer cells exhibited abundant Id-1, Id-2, and Id-3 immunoreactivity," and Id-1 and Id-2 protein was increased significantly in the cancer cells by comparison to the respective controls, mirroring the overexpression at the mRNA level. Thus, the authors report that in both cell lines and tissue samples, increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 8). In a previous study, the authors investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Mizrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 9) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55 kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 10), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants' assertion that changes in mRNA level, e.g. a decrease, lead to a corresponding change in the level of the encoded protein, e.g. a decrease.

In an article by Guo and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 11) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome(ARDS) by examining the expression of MIF mRNA and protein in lung tissue in ARDS and normal persons. *Id.* at Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lungs. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lungs." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular gene, e.g. an increase, generally leads to a corresponding change in the level of protein expression, e.g. an increase.

These studies are representative of numerous published studies which support Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit herewith an additional 70 references (abstracts attached as Exhibit 12) which support Applicants' assertion.

In addition to these supporting references, Applicants also submit herewith additional references which offer indirect support of Applicants' asserted utility. As discussed in detail above, Applicants have challenged the relevance of references such as Haynes *et al.*, Gygi *et al.*, and Chen *et al.* which do not attempt to examine the correlation between a change in mRNA level and a change in the level of the corresponding protein level. Because the PTO continues to

rely on these references, Applicants are submitting references which report results that are contrary to the PTO's cited references and offer indirect support for Applicants' asserted utility.

For example, in an article by Futcher *et al.* (Mol. Cell Biol. 1999; 19(11):7357-68) (abstract attached as Exhibit 13) the authors conducted a study of mRNA and protein expression in yeast which was nearly identical to the one conducted by Gygi *et al.* and reported in Haynes *et al.* Contrary to the results of the earlier study by Gygi, Futcher *et al.* report "a good correlation between protein abundance, mRNA abundance, and codon bias." *Id.* at Abstract.

In a study which is more closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 14) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Similarly, in an article by Papotti *et al.* (Virchows Arch. 2002; 440(5):461-75) (abstract attached as Exhibit 15) the authors examined the expression of three somatostatin receptors (SSTR) at the mRNA and protein level in forty-six tumors. *Id.* at Abstract. The authors report a "good correlation between RT-PCR [mRNA level] and IHC [protein level] data on SSTR types 2, 3, and 5." *Id.*

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 16) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 17) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 18) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC)

B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression commensurate with the low protein expression level" and that in DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good correlation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 19) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases)." *Id.* at Abstract. "There was a good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO's arguments. Applicants submit herewith 26 additional references (abstracts attached as Exhibit 20) which also support Applicants' assertion in that the references report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

In summary, Applicants submit herewith a total of 113 references in addition to the declarations and references already of record which support Applicants' asserted utility, either directly or indirectly. These references support the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein.

Applicants also previously submitted the Polakis Declaration in support of their position that in general, changes in mRNA levels correlate with changes in protein levels. (Submitted as Exhibit 6 in the Amendment and Response mailed April 7, 2005). In response to the Polakis Declaration, the PTO argues that there is allegedly "no evidentiary support" of Dr. Polakis' conclusion that increased mRNA levels are predicative of corresponding increased levels of the encoded polypeptide. *Examiner's Answer* at 37.

Without acquiescing to the propriety of this rejection, and merely to expedite prosecution in this case, Applicants submit herewith as Exhibit 21 a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says

"[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions.

The case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument" *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996)(quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner" *Id.* at 1583. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines[1] which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Part IIB, 66 Fed. Reg. 1098 (2001).

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.,* abstracts attached as Exhibit 22). However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting

Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

In conclusion, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1926 mRNA is differentially expressed in esophageal tumors as compared to normal esophagus tissue, the PRO1926 polypeptide will likewise be differentially expressed in esophageal tumors. This differential expression of the PRO1926 polypeptide makes the claimed polypeptides useful as diagnostic tools for cancer, particularly esophageal cancer.

Utility – Conclusion

Applicants remind the PTO that the evidence supporting utility does not need to be direct evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (same); *Nelson v. Bowler*, 626 F.2d 853, 857, 206 U.S.P.Q. 881 (C.C.P.A. 1980) (same). In addition, utility need only be shown to be "more likely than not true," not to a statistical certainty. *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also maintains its rejection of pending Claims 6-8 and 11-17 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. *Examiner's Answer* at 47. In addition, the PTO makes the conclusory statement that even if the specification taught how to use the PRO1926 polypeptide, enablement would not be commensurate in scope with Claims 14-

17, which encompass percent variants and fragments of SEQ ID NO:136, because there is no structural or functional information provided in the specification. *Examiner's Answer* at 47.

The PTO has Failed to Establish a Reasonable Basis to Question the Enablement of the Pending Claims

The PTO has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See M.P.E.P.* § 2164.04. It is incumbent for the PTO "to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Id.* (quoting *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). This can be done "by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact." *Id.*

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Turning to the PTO's other arguments, in the final Office Action, the PTO makes the conclusory statement that enablement is not commensurate in scope with claims "because there is no structural or functional information provided in the specification." *Final Office Action* at 15.

The PTO maintains the position that "the skilled artisan would not be able to determine, without undue experimentation, the structural conformation and function of PRO1926 variants based upon linear amino acid sequences only." *Examiner's Answer* at 50-51. The PTO then argues that Applicants have "provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the position in the PRO1926 protein which are tolerant to change (e.g., such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions," such that the polypeptides still retain catalytic activity. *Examiner's Answer* at 50.

As an initial matter, Applicants note that pending Claims 6 and 12-13 do not recite percent amino acid sequence identity as a limitation. These claims are directed to peptides of the disclosed sequence, with or without the disclosed signal peptide, and fusion proteins thereof which would be optimal, for example, in making antibodies. Therefore, any arguments based on a failure to enable variants are not applicable to pending Claims 6 and 12-13.

Regarding the enablement of Claims 14-17, Applicants disagree with the PTO's assertion that the skilled artisan could not, without undue experimentation, determine information regarding the structural conformation of PRO1926 sufficient to make and use variants of PRO1926 that "can be used to generate an antibody to specifically detect the polypeptide of SEQ ID NO:136 in esophagus tissues." Several publicly available software programs are designed for the particular purpose of predicting secondary and tertiary protein structure based on primary amino acid sequence data. By way of example, links to over thirty publicly available software programs for the prediction of secondary and tertiary protein structure are found at <http://www.expasy.org/tools/>(last visited April 19, 2006). Furthermore, Applicants maintain that it is well known that primary amino acid sequence data can be used to predict immunogenic regions of proteins. *Sutcliffe et al.*, Science (1983) 219:660-666 (attached as Exhibit 23) teaches that

> Peptides capable of eliciting protein-reactive serums are frequently represented in the primary sequence of a protein, can be characterized by a set of simple chemical rules, and are confined neither to immunodominant regions of intact proteins nor to the amino or carboxy terminals. As such, synthetic peptide immunogens are valuable for eliciting reagents with predetermined specificity that can be used for basic research. *Sutcliffe* at Abstract.

Importantly, Sutcliffe *et al.* also state that "by following simple rules, one can in general select peptides that will elicit antibodies reactive with intact proteins." *Sutcliffe et al.* at 661-662. In other words, Sutcliffe *et al.* demonstrates that at the time the instant application was filed, the skilled artisan would not have to undertake undue experimentation to make and use the claimed polypeptides.

Applicants' specification teaches in detail how to make the claimed polypeptides, including variants thereof, and antibodies which specifically bind PRO1926. Likewise, the specification provides sufficient guidance as to how to use the claimed polypeptides. Thus, contrary to the PTO's statement, there is significant guidance how to make and use the claimed

polypeptides. In addition, as the disclosure and references cited in the specification make clear, the production of polypeptides, polypeptide variants, and specific antibodies is a predictable and well established aspect of the biological sciences. *See, e.g., In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988) (reversing the Board's decision of non-enablement and holding that as of 1980, undue experimentation was not required to make high-affinity monoclonal antibodies to a target peptide).

In conclusion, the PTO's rejection based on lack of utility has been addressed above, and the PTO has otherwise failed to meet its burden to establish a reasonable basis to question the enablement provided for the claimed invention –statements regarding the inability to generate structural information from amino acid sequence data, are simply not sufficient. Given the skill in the art and the disclosure of how to make and use the claimed polypeptides, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO maintains the rejection of pending Claims 14-17 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement for the reasons set forth in the previous Office Actions. Briefly, the PTO asserts the "Applicants have not described or shown possession of all polypeptides 95-99% homologous to SEQ ID NO:136, that still retain the function of SEQ ID NO: 136." *Examiner's Answer* at 54.

The PTO has Failed to Meet Its Initial Burden of Rebutting the Presumption that the Pending Claims are Adequately Described

To overcome the presumption that the claimed subject matter is adequately described, the PTO must present "evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 U.S.P.Q. at 97." *M.P.E.P.* § 2163.04.

Whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention.

An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

The pending claims are related to isolated polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO:136, and satisfying the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:136 in esophagus tissue samples."

Applicants maintain that there is no substantial variation within the species which fall within the scope of the amended claims, which require at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO:136. Applicants note that the pending claims are analogous to the claims discussed in Example 14 of the written description training materials. In Example 14, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences (*i.e.*, at most, they differ from SEQ ID NO:136 by 12 amino acids) and must share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO:136 in esophagus tissue samples.

In Example 14, a single polypeptide sequence was provided, and the claims were directed to variants that were at least 95% identical to that sequence. The PTO states the facts of the instant application are not analogous to Example 14 in the Revised Interim Written Description Guidelines. Specifically, the PTO asserts that in Example 14, the claimed protein variants "have a high percent sequence identity in combination with a specific functional limitation" and that "methods of generating variants of the protein that have 95% identity and retain its activity are conventional in the art" because "deletions substitutions, insertions, and additions of uncritical amino acid residues would not affect the enzyme activity." *Examiner's Answer* at 57. The PTO

argues that "for inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." *Examiner's Answer* at 58.

The PTO's position is inconsistent with the most recent decisions by the Federal Circuit. In a recent Federal Circuit decision, *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004), the Court stated:

> [W]e agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious. ... A claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants.
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> Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *Id.* (emphasis added).

The Court did not require the Applicants in *Wallach* to actually make and individually describe all of the vast number of sequences which encode the disclosed sequence. This is in spite of the fact that there is no possibility that even the most skilled artisan could "envision the detailed chemical structure of all or a significant number" of encompassed polynucleotides. Because it is routine to convert between amino acid sequences to nucleic acid sequences, disclosure of a single amino acid sequence was sufficient to describe the very large genus of nucleic acids which could encode the sequence.

The facts in *Wallach* are very similar to the instant case. Here, Applicants have disclosed SEQ ID NO:136, and claim polypeptides which are homologous to it and have the functional limitation of having the ability to generate antibodies which can be used to specifically detect

SEQ ID NO:136 in esophagus tissue samples. It is routine in the art to create polypeptides which have at least 95% or 99% sequence identity to SEQ ID NO:136 – it is just as predictable and easy as creating all of the nucleic acids which encode a particular amino acid sequence. Similarly, it is well within the skill of those in the art to determine which polypeptides can be used to make the recited antibodies. This structure/function combination is sufficient to describe the claimed polypeptides. The *Wallach* opinion makes clear that there is no need to list each individual sequence within the genus to adequately describe the genus.

In further arguing that Example 14 is inapplicable to the presently claimed polypeptides, the PTO states that the polypeptide in Example 14 possess a catalytic activity, but "in the instant case, the polypeptide of PRO1926 has no utility and has no disclosed function... [f]urthermore, the specification and the claims do not disclose the identification of any particular portion of the PRO1926 structure that must be conserved in order to conserve the required function." *Examiner's Answer* at 57. In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Example 14, however, is not limited to those activities that are catalytic – rather, it applies to polypeptides having homology to a disclosed sequence and sharing the same function. In the instant application, it is well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. In addition, the specification discloses how to make antibodies which specifically detect the polypeptide of SEQ ID NO:136 in esophagus tissue samples. Like Example 14, the genus of polypeptides that have at least 95% or 99% amino acid sequence identity to the disclosed sequences and share the same activity will not have substantial variation. Accordingly, the claimed polypeptides are fully described by the specification.

Applicants assert that principles for designing polypeptides with desired antigenic properties were well known in the art at the time of filing of the instant application. As discussed above, Sutcliffe *et al.* is illustrative of the state of the art regarding antibody technology at the time the instant application was filed. Sutcliffe *et al.* demonstrates that simple chemical rules can be used to determine antigenic regions of polypeptides given the primary amino acid sequence. *See*, Sutcliffe *et al.* at Abstract. Further, Sutcliffe teaches that "longer, soluble peptides, especially those containing proline residues, were effective." Sutcliffe at 661, left column. Sutcliffe goes on to state that "by following simple rules, one can in general select

peptides that will elicit antibodies reactive with intact proteins." Sutcliffe at 661-662. Thus, Sutcliffe exemplifies that one skilled in the art knew "simple rules" for determining which polypeptides can be used to generate an antibody that can be used to specifically detect a particular polypeptide. Sutcliffe, teaches that one skilled in the art knew how to determine which polypeptides can be used to generate an antibody that can be used to specifically detect a particular polypeptide. Thus, in view of the knowledge in the art and the teachings in Applicants' disclosure, one skilled in the art would have known what polypeptides can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:136 in esophagus tissue samples.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:136, by specifying a high level of amino acid sequence identity, by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." The knowledge in the art, as exemplified by Sutcliffe et al. supports this conclusion, and the references cited by the Examiner cannot support an assertion to the contrary. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §102(b) – Anticipation

The PTO maintains the rejection of pending Claims 6-8, and 11-17 as anticipated under 35 U.S.C. § 102(b) by Valenzuela *et al.* (WO 00/55375) (hereinafter Valenzuela), which was published September 21, 2000. The PTO states that Valenzuela discloses an amino acid sequence that has 100% identity to SEQ ID NO: 136 of the instant invention. Applicants respectfully traverse.

To be anticipated under 35 U.S.C. § 102(b), the invention must be patented or described in a printed publication "more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). Applicants submit that Valenzuela does not anticipate any of the pending claims because it was not published more than one year prior to the date of the

instant application for patent in the United States. The instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/170262 filed 12/9/1999.

Applicants submit that for the reasons stated above, the claimed polypeptides have a credible, substantial, and specific utility. Therefore, the instant application is entitled to a priority date of at least August 24, 2000. Valenzuela was published September 21, 2000, which is not more than one year prior to August 24, 2000, and therefore Valenzuela is not prior art under 35 U.S.C. § 102(b). Applicants request that the PTO reconsider and withdraw the rejection under 35 U.S.C. § 102(b) based on Valenzuela.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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